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Transition Metal-Catalyzed Regioselective and Stereoselective Aminochlorination of Cinnamic Esters

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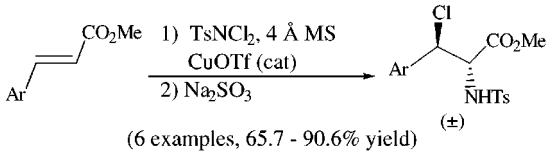
ABSTRACT



(6 examples, 65.7 - 90.6% yield)

A new aminohalogenation process has been developed for the synthesis of vicinal haloamine derivatives using cinnamic esters as substrates. The reaction was performed in CH_3CN using $ZnCl_2$ or $Cu(OTf)_2$ as catalyst and *N*,*N*-dichloro-*p*-toluenesulfonamide as chlorine/nitrogen source. Good to excellent yields and regio- and stereoselectivities have been obtained. The stereochemistry was unambiguously determined by transforming one of the products to a known sample.

The vicinal haloamine functionality presents a very useful structural moiety in synthetic organic chemistry.[1] Even though some progress has been made in developing efficient synthetic approaches to this functionality,[2−7] very few reports about the heterolytic additions of nitrogen and chlorine to olefins have appeared in the past decade. Furthermore, the application of this process in organic chemistry has not been very successful yet.[1] The study of highly regioselective and stereoselective aminohalogenation of olefins still remains important and challenging.

Cinnamic esters are believed to be among the most synthetically useful substrate classes[8] for olefin oxidative reactions which include catalytic asymmetric dihydroxylation,[9a,b] epoxidation,[10] aziridination,[8,9c,11] aminohydroxylation,[12] etc. Obviously, these olefin substrates should also be subjected to a vicinal aminochlorination process because the resulting chlorinated amino acids can be converted to numerous useful organic molecules by replacing chlorine atom with a series of nucleophiles. Surprisingly, a successful cinnamic ester-based aminochlorination has not been developed so far. Recently, we tried to render this reaction by using the $CrCl_2$-promoted addition of *N*-chlorocarbamates[4,5] and direct addition of *N*,*N*-dichlorosulfonamides or dichlorocarbamates[6] onto cinnamic esters. Unfortunately, no haloamine product

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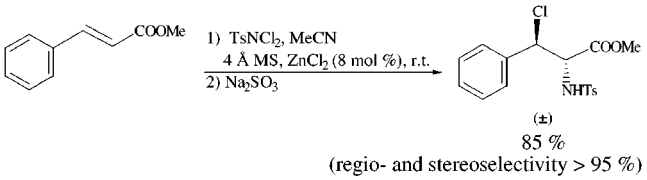
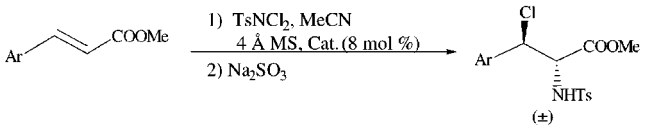
Scheme 1. Transition Metal-Catalyzed Aminochlorination of Methyl Cinnamate[15]



was obtained under these known conditions. In this report we describe a successful transition metal-catalyzed aminochlorination of cinnamic esters by using *N*,*N*-dichloro-*p*-toluenesulfonamide as the nitrogen source. The reaction is represented in Scheme 1 with the results summarized in Scheme 2 and Table 1.

Scheme 2

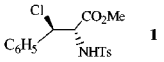
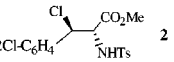
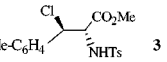
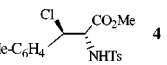
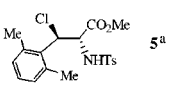
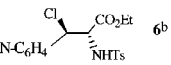


N,*N*-Dichloro-*p*-toluenesulfonamide ($TsNCl_2$) employed in this system was prepared by the treatment of *p*-toluenesulfonamide with commercial bleach, followed by CH_3COOH acidification. At first, a series of solvents such as CH_2Cl_2, $CHCl_3$, THF, benzene, toluene, MeCN, etc. were tried for the direct aminochlorination without success. Transition metal compounds were then screened to catalyze the reaction. These compounds include Hg_2Cl_2, $NiCl_2$, $ZnCl_2$, $SnCl_2$, $RuCl_3$, $PdCl_2$, $FeCl_2$, $Cu(OTf)_2$, etc. Among these catalysts, we found that $ZnCl_2$ and $Cu(OTf)_2$ can efficiently catalyze the aminochlorination only when acetonitrile was used as the solvent. It is interesting to note that little or no products were obtained in all other solvent systems. More interestingly, both regioselectivity and stereoselectivity were controlled very well in acetonitrile. Essentially, only the *trans*-β-chloro α-amino isomer was observed by ^1H NMR analysis of the crude products for most cases (**1**−**4** and **6**) in Table 1. For example **5**, the modest stereoselectivity observed indicated *trans*:*cis* = 4:1 and 5:1 for $ZnCl_2$ and $Cu(OTf)_2$, respectively. For most cases in Table 1, yields were improved by about 5−10% by addition of 4 Å molecular sieves to the reaction systems.

For non-metal-catalyzed aminochlorination processes, both ionic and radical mechanisms were proposed.[3b,c,6−7] The stereoselectivity of haloamine products depends on different olefin substrates. For example, the reaction of *N*,*N*-dichloro-4-toluenesulfonamide with (*E*)-stilbene resulted in a mixture of *anti* and *syn* adducts. However, the same reaction using indene as the substrate gave predominantly *trans* adduct. The stereochemistry of the products in Table 1 indicates a possible bridged chloronium ion mechanism in the present catalytic process. Lewis acidic catalysts could coordinate to the oxygen atom of the sulfonyl group to activate the N−Cl bond prior to the addition reaction.

The regioselectivity and *anti*-selectivity were determined by the conversion of product **1** to a known sample which was synthesized by using the CT-based Sharpless AA

Table 1. Results of $ZnCl_2$- and $Cu(OTf)_2$-Catalyzed Aminochlorination of Methyl Cinnamates[16]

Ar	product (±)		m.p.(°C)	yield (%)	
				$ZnCl_2$	$Cu(OTf)_2$
C_6H_5		**1**	142 - 144	85.0	80.0
2-Cl-C_6H_4		**2**	136 - 138	52.0	65.7
2-Me-C_6H_4		**3**	132 - 134	71.2	74.0
4-Me-C_6H_4		**4**	143 - 145	75.5	71.4
		**5**[a]	oil	84.3	79.8
4-NO_2-C_6H_4		**6**[b]	oil	78.4	90.6

[a] The yields of two isomers which were difficult to separate by column chromatography, *trans*/*cis* = 4/1 and 5/1 for $ZnCl_2$ and $Cu(OTf)_2$ respectively. [b] The reaction needs 2 equiv of $TsNCl_2$ and 48 h. Otherwise, the standard conditions.

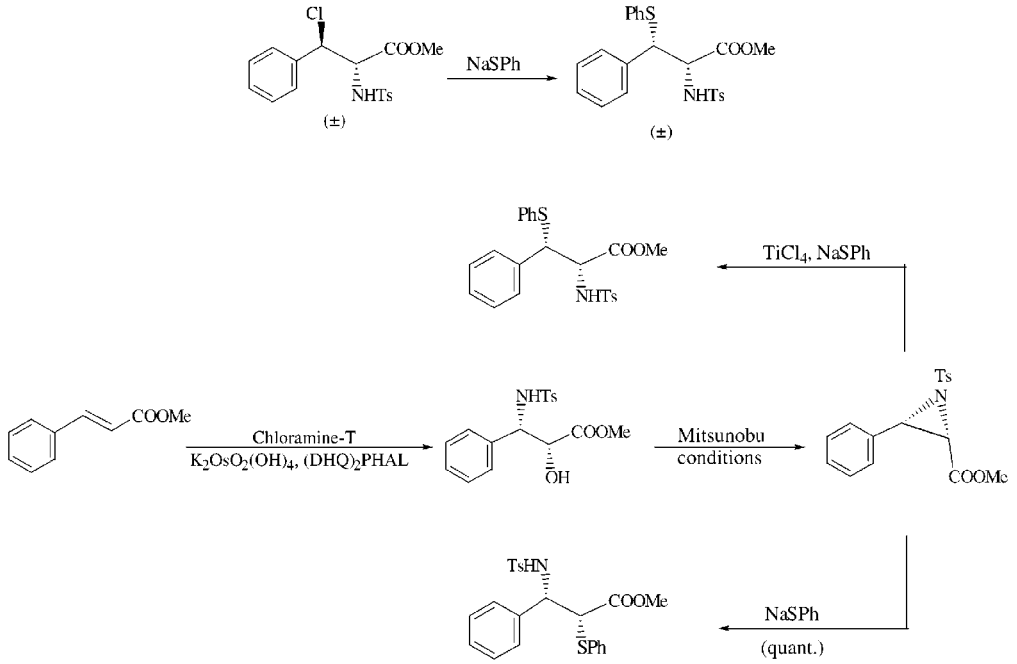
(13) (a) Mitsunobu, O. *Synthesis*, **1981**, 1. For an alternative AA-based *cis*-aziridine formation, see: (b) Rubin, A. E.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2637.

(14) A similar titanium-mediated epoxide opening see: Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560.

(15) **Typical Procedure: $ZnCl_2$-Catalyzed Aminochlorination Reaction of Methyl *trans*-Cinnamate with *N*,*N*-Dichloro-4-Toluenesulfonamide As Described in Scheme 1.** Into a dry vial was added methyl cinnamate (81.0 mg g, 0.50 mmol) and freshly distilled acetonitrile (1.5 mL). The reaction vial was immersed in a room temperature bath, and loaded with freshly activated 4 Å molecular sieves (150 mg), $TsNCl_2$ (144 mg, 0.60 mmol, 1.20 equiv), and $ZnCl_2$ (5.50 mg, 8 mol %). The resulting solution in the capped vial was stirred at room temperature for 22 h without argon protection. The reaction was finally quenched by dropwise addition of saturated aqueous Na_2SO_3 solution (2 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with 10% aqueous ammonia and brine, dried over anhydrous magnesium sulfate, and concentrated to dryness. Purification by flash chromatography (EtOAc/hexane, 1/3, v/v) provided *trans*-methyl 3-chloro-2-(*p*-toluenesulfonamido)-3-phenylpropionate **1** (0.129 g, 85.0% yield) as colorless solid: mp 142−144 °C; ^1H NMR (200 MHz, DMSO-d_6) δ 8.75 (d, J = 9.93 Hz, 1 H), 7.24−7.52 (m, 9 H), 5.04 (d, J = 10.3, 1 H), 4.29 (t, J = 10.3, 1 H), 3.35 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 142.8, 137.3, 136.7, 129.4, 128.9, 128.5, 128.2, 126.3, 61.1, 60, 52.0, 21.0.

(16) ^1H NMR data of the pure products in Table 1 (200 MHz, $CDCl_3$): **2** δ 8.91 (d, J = 10 Hz, 1H), 7.30−7.53 (m, 8H), 5.42 (d, J = 10, 1H), 4.64 (t, J = 10, 1H), 3.35 (s, 3H), 2.37 (s, 3H); **3** δ 8.77 (d, J = 10 Hz, 1H), 7.20−7.58 (m, 8H), 5.22 (d, J = 10.7, 1H), 4.48 (t, J = 10.4, 1H), 3.31 (s, 3H), 2.36 (s, 3H); **4** δ 8.74 (d, J = 10 Hz, 1H), 7.06−7.50 (m, 8H), 4.99 (d, J = 10.4, 1H), 4.25 (t, J = 10, 1H), 3.35 (s, 3H), 2.35 (s, 3H), 2.25 (s, 3H); **6** δ 8.92 (d, J = 9.8 Hz, 1H), 8.04 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.2 Hz, 2H), 5.18 (d, J = 10.3, 1H), 4.34 (t, J = 10, 1H), 3.39 (s, 3H), 2.29 (s, 3H).

Scheme 3. Stereochemistry Determination by Synthetic Conversions to a Known Sample



reaction[12,13] (Scheme 3). In this procedure, the Sharpless AA product, (2*R*,3*S*)-methyl 2-hydroxy-3-(*p*-toluenesulfonamido)-3-phenylpropionate, was first subjected to the Mitsunobu conditions to give a *cis*-*N*-tosylaziridine.[13] This transformation can also serve as a new efficient approach to *cis*-*N*-tosylaziridines. $TiCl_4$-promoted ring opening of the resulting *cis*-*N*-tosylaziridine with PhSNa gave (2*R*,3*S*)-methyl 3-(phenylthio)-2-(*p*-toluenesulfonamido)-3-phenylpropionate as the major isomer.[14] The minor regioisomer was identical to the product of a similar ring opening in the absence of $TiCl_4$ in which the nucleophilic substitution took place quantitatively on the α-position of aziridine. Mass spectroscopy analysis of **1** also further supported the assigned regioselectivity in which two major species, $[C_6H_5CHCl]^+$ and [TsNHCHCOOMe]$^+$, were clearly observed.

In conclusion, a novel regio- and stereoselective aminochlorination of alkyl cinnamates has been established by using $ZnCl_2$ and $Cu(OTf)_2$ as catalysts and *N*,*N*-dichloro-4-toluenesulfonamide as an oxidative nitrogen source. The reaction is easy to perform at room temperature in any vial of appropriate size. The stereochemistry was unambiguously assigned by synthetic conversions to a known sample and further confirmed by MS spectroscopy. Similar transition metal/ligand-catalyzed aminohalogenation processes will be next explored to ascertain the possibility of its asymmetric version.

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